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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,554	12/22/2004	Lars Siim Madsen	2815-0287PUS1	8395

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EXAMINER	
STOCKTON, LAURA LYNNE	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 06/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,554	MADSEN ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 24-41 are pending in the application.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The Examiner has considered the Information Disclosure Statement filed on December 22, 2004.

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Objections

Claim 41 is objected to because of the following informalities: according to MPEP 608.01(m), each claim should begin with a capital letter and end with a period. The "A" before "benzimidazole-2-one" and "therapeutic" should be lower case as well as the "I" in "Instructions".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in

such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

Applicants are claiming methods for the treatment, prevention or alleviation of a disease or a disorder or

a condition of a mammal by administering a compound of formula (I), optionally in combination with a therapeutic agent. See, for example, instant claim 32. From the reading of the specification, it appears that Applicants are asserting that the embraced compounds, because of their mode action which involves the modulation of BK_{Ca} channels, would be useful for treating, preventing or alleviation of numerous diseases and disorders such as cystic fibrosis, obstructive or inflammatory airway disease, cardiovascular disease, etc. Additionally, starting on page 7, line 26 of the instant specification, "therapeutic agent" is discussed, which expression embraces all antineoplastic agents, all chemotherapeutic agents, etc.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that K^+ channelopathies remains highly unpredictable. Lawson

{Expert Opinion on Investigational Drugs (2000), 9(10), pages 2269-2280} states "Potassium (K^+) channel openers (KCOs), agents that increase or maintain an increased openness of K^+ channels, mimic a fundamental physiological mechanism for the reversal or prevention of depolarizing activity of membranes". Lawson states, "Initial potential therapeutic targets of specific K^+ channel subtypes can be identified for drug discovery efforts directed, at least, to neurological diseases and indications. The challenge ahead cannot, however, be over stated due to the complexity presented by individuals with mutations in the same gene expressing different phenotypes or conversely, the same phenotype being caused by mutations in different genes. Ultimately, accurate molecular diagnostics will be needed to develop effective therapies and accurate prognoses". Lawson further states "The ubiquitous nature of K^+ channels, however, may present limitation of the utility of even highly specific KCOs by

introducing modulation of the activity of tissues distant (e.g., peripheral) from the site of pathophysiological origin".

Further, Balinsky, Ph.D., et al. {Journal of Pediatric Health Care, Vol. 18, No. 1, pages 30-34, (January/February 2004)} state that Cystic Fibrosis (CF) is a chronic, progressive and frequently fatal disease which primarily affects the respiratory and gastrointestinal system. Balinsky, Ph.D., et al. also state "CF testing will not eliminate or cure the condition but will substantially benefit the affected persons". Therefore, there is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present and the presence or absence of working examples

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the numerous diseases or disorders claimed herein. That a single class of compounds can be used to treat, prevent or alleviate all diseases embraced by the claims is an incredible finding for which Applicants have not provided supporting evidence. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating, preventing or alleviating all diseases, disorders and conditions by administering the instant claimed compounds.

The breadth of the claims

The breadth of the claims is a method for the treatment, prevention or alleviation of all diseases, disorders or conditions responsive to modulation of BK_{Ca}

channels by administering a compound of formula (I), optionally in combination with a therapeutic generically embraced in the claim language.

The quantity of experimentation needed

The nature of the pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities for each of the diseases, disorders and conditions instantly claimed. Further, "therapeutic agent" is so broadly disclosed and defined in the specification with specific examples given only for a "chemotherapeutic agent". The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to testing all diseases, disorders and conditions generically embraced in the claim language, and when faced with the unpredictability of the pharmaceutical art. Thus, factors such as "sufficient working examples", "the

level of skill in the art" and predictability, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

The level of the skill in the art

Even though the level of skill in the pharmaceutical art is very high, based on the unpredictable nature of the invention and state of the prior art and lack of guidance and direction, one skilled in the art could not use the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29, 30, 32 and 36 lack antecedent basis from claim 24 since a pharmaceutically acceptable salt of the compound is not found in claim 24.

In claim 36, the phrase "The method of a benzimidazole-2-one derivative according to claim 24" is indefinite because claim 24 is directed to a compound and not a method.

The showing in the specification on pages 14-19 has been considered but has not been found persuasive because Applicants did not compare the closest prior art compounds. Example 10 and Example 14 in EP 477,819 are closer structurally {5-fluoro in the prior art verses 5-chloro of instant Example 1 found on page 13 of the instant specification} than the Reference compound used in the comparative study, which has a 5-

trifluoromethyl group on the benzimidazolone ring. Applicant relying upon comparative showing to rebut prima facie case must compare his claimed invention with the closest prior art. *In re Holladay*, 199 USPQ 516, 1978.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olesen et al. {EP 477,819} and Olesen et al. {EP 617,023}, each taken alone or in combination with each other.

Determination of the scope and content of the prior art (MPEP §2141.01)

Applicants claim benzimidazolone compounds. Olesen et al. '819 (formula I in column 2 and especially Examples 10 and 14 in columns 15 and 16, respectively) and Olesen et al. '023 (the formula in column 2; the methods in column 3; and the compositions in columns 6-9) each teach benzimidazolone compounds that are structurally similar to the instant claimed compounds.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the compounds of the prior art and the compounds instantly claimed is that the instant claimed compounds are generically described in the prior art.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., K^+ channel openers).

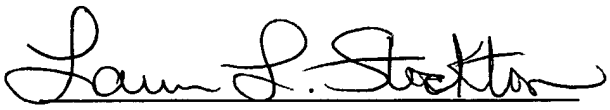
One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating diseases which can be treated by opening cell membrane potassium channels in mammals such as hypertension, asthma, ischemia, convulsions, etc. Since each of the prior art references teach that the benzimidazolone compounds have K^+ channel opener activity, the combination of the prior art references would also teach the instant claimed invention. The instant claimed invention would have been suggested to

one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.



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